CASE REPORT

Atypical presentation and management of fibrodysplasia ossificans progressiva

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SUMMARY

We report a case of an 18-year-old woman, with bilateral acute inflammatory pain on the hip area, during the premenstrual period, and progressive increase in volume and rigidity of both hips. Bilateral exuberant soft tissue calcifications were present on the radiographic exams, and the patient also presented with bilateral short-length hallux valgus. A heterozygous mutation in the protein kinase domain of *ACVR1* gene was found, allowing the diagnosis of fibrodysplasia ossificans progressive. Due to the relation between the disease flares and the premenstrual period, the patient was put into a chemically induced amenorrhea, with no new inflammatory crises since.

This case illustrates the importance of an accurate diagnosis to prevent unnecessary diagnostic procedures, as well as the need to develop specific treatment strategies to address each patient's particular needs.

BACKGROUND

Fibrodysplasia ossificans progressiva (FOP) is a rare and incapacitating autosomal-dominant disease affecting connective tissue by defectively inducing endochondral osteogenesis.[1] Classical signs of this condition are hallux or thumb deformities and progressively debilitating heterotopic ossification, with normal bone formation in extraskeletal sites, such as soft tissues around the neck and shoulders.[2] Confusion with tumours is common, which may lead to aggressive and invasive diagnostic or excision techniques that will only accelerate the rate of bone growth.[3]

Atypical forms of FOP have also been described. These forms may present in two ways: classical FOP features in addition to one or more atypical features; or major variations of the two classically defining features.[4]

Managing this condition may be a challenge, and care must be taken to identify any trigger events that lead to soft tissue bone formation to develop a specific preventive strategy for each patient.

CASE PRESENTATION

We present an 18-year-old young woman, born from an incestuous relation, with prior history of oligophrenia, alopecia and bilateral hearing impairment. Patient was otherwise healthy until her menarche when she began experiencing acute inflammatory pain on the hip area during the premenstrual period, with progressive increase in volume and rigidity of both hips.

She presented with a waddling gait, limited and painful mobility of both hips (0-0-75°) with hard and prominent bilateral masses (figure 1). There were no records of any traumatic events.

INVESTIGATIONS

Plain pelvic radiography (figure 2) and CT scan (figure 3) showed exuberant soft tissues calcifications, enveloping both hips and thighs. There was no involvement of the surrounding skeleton, and no other anomalous tissue was found on the calcifications location.

Patient was otherwise fit, with no recent history of weight loss, fever or other systemic signs of illness.

Due to these complaints, patient was referred to the orthopaedics consult for evaluation and to schedule a biopsy, as her family's physician suspected of a neoplastic lesion. However, due to the characteristics of the patient's feet (short hallux valgus with malformation of the first metatarsal) and of the anomalous masses, we considered there was a higher probability of FOP than of a malignant tumour.

Decision was made to send the patient for a genetics appointment, where a heterozygous mutation in the protein kinase domain of *ACVR1* gene, identified as the genetic cause of FOP, was found.

DIFFERENTIAL DIAGNOSIS

Treatment

Due to the uncommon onset of these painful crises and a narrow correlation between the complaints and the premenstrual period, the case was discussed with the gynaecology department. Consideration was given to muscular endometriosis being the possible cause for the localised heterotopic endochondral bone formation. Unfortunately, no evidence was found supporting that theory, probably due to heterotopic bone formation preventing visualisation of any other anomalous tissues.

Given the contraindication for any invasive procedure, decision was made to chemically induce amenorrhea to control the inflammatory crises. Other usual measures for FOP were also taken, namely caretaker education for prevention of falls and other traumatisms, as well as usage of corticosteroids during a short time period and non-steroid anti-inflammatory drugs whenever pain occurred.

OUTCOME AND FOLLOW-UP

At 3 years' follow-up, no new painful crises have been reported, with the exception of two isolated traumatic events.

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Figure 1 Anterior and posterior aspect of the patient's pelvis, at physical examination, with prominent bilateral masses in the hip area.

DISCUSSION

FOP is a debilitating condition that usually displays its first symptoms by the first decade of life, with sporadic episodes of painful soft tissues swelling, usually triggered by trauma, muscle fatigue or influenza-like illnesses, promptly followed by bone formation.[5]

With a prevalence of one case in every two million people, this rare disease usually occurs as a new mutation in the protein kinase domain of *ACVR1* gene, leading to deregulation of specific bone morphogenetic proteins and destabilising connective tissue progenitor cells.[6 7]

FOP is often misdiagnosed by the untrained physician, and confused with conditions such as soft tissue sarcomas, even when classical clinical features are present. Aggressive and unnecessary diagnostic methods, such as biopsies, are commonly performed in these situations, leading not only to patient discomfort but also to an increase in local disease progression. Therefore, most authors advise against performing any surgical or invasive procedure in these patients.[8]

Identification of atypical forms of FOP, as the one depicted on this report, has important diagnostic and therapeutic implications. Kaplan *et al*[4] published a series of 12 atypical cases, some of which with a late onset, development of sparse thin hair and cognitive impairment. Although the inflammatory cascade plays a critical role in FOP,[9] our research retrieved no report of heterotopic ossification triggered by the inflammatory crises that may usually occur in the premenstrual period.

This case was a therapeutic challenge since there was no traumatic cause related to the disease flares that could be prevented. Nevertheless, a multidisciplinary approach was essential to come up with a definitive diagnosis and a therapeutic solution that provided successful control of the premenstrual inflammatory crises.

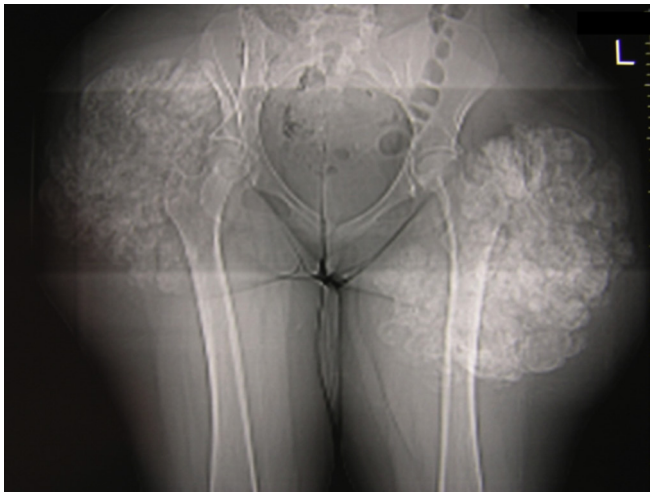

Figure 2 Plain pelvic radiography, showing bilateral calcified masses, around both hips.

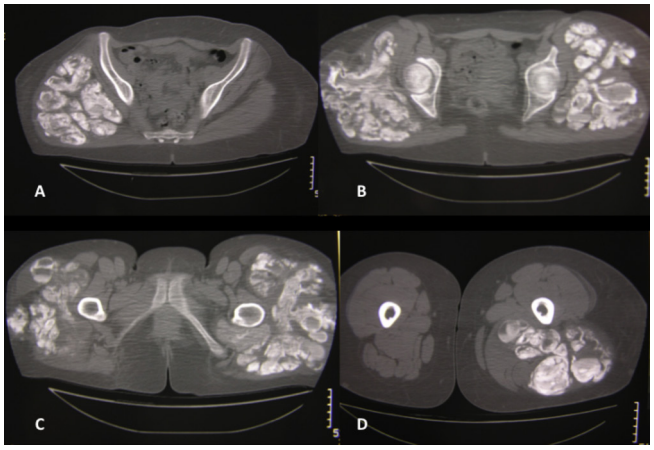

Figure 3 Axial images of CT scan, showing evidence of heterotopic soft tissue calcification, without any involvement of the surrounding skeleton (part figures A, B, C and D show the extension of the heterotopic calcification).

Learning points

- Fibrodysplasia ossificans progressiva (FOP) is a debilitating condition that presents with endochondral osteogenesis of the soft tissues, usually following trauma or other conditions that trigger an inflammatory response.
- Biopsy of FOP lesions or other invasive procedures must be avoided at all costs, as they will lead to worsening of this disease.
- It is possible to partially control FOP with a strategy that addresses the specific trigger for the inflammatory response that leads to bone formation.

Contributors All authors contributed equally to patient's diagnostics, treatment and follow-up. AG and JA wrote the case report and AM was responsible for reviewing the manuscript.

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